Author’s response to reviews

Title: Comparison of transcatheter aortic valve implantation with other approaches to treat aortic valve stenosis: a systematic review and meta-analysis

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Response to reviewer comments

Dear Professor Troiano,

We would like to thank the reviewers for the valuable feedback that we received in response to our submission. We have revised the manuscript accordingly and are confident that we addressed all the points that the reviewers raised. Below please find our responses to their comments. We used track-changes in the revised manuscript.

If you have any questions, please don’t hesitate to contact us anytime.

Sincerely,

Gernot Wagner

on behalf of the authors
Reviewer #1

Reviewer’s comment:

By reading the abstract, we got a clear message, that there is no difference between TAVI and SAVR. I suggest to modify the article name by highlighting this result, for example: No difference in outcome between…. Keeping "a systematic review and meta-analysis"

Authors’ response:

Many thanks for your suggestion. Reviewer #2 also suggests a change of the title (“Comparison of transcatheter aortic valve implantation with other approaches to treat aortic valve stenosis: a systematic review and meta-analysis”). For the revised manuscript, we adopted the title of Reviewer #2 because we think it is more in line with the journal’s guidance. However, we’d be happy to revise the title if the editors would like us to do so.

Reviewer’s comment:

I would ask the author about the PROSPERO registration code. If not applicable, I would just ask to remind for their future publications.

Authors’ response:

Thank you for raising this issue. We are aware that preceding registration of systematic reviews in PROSPERO is important for transparency, quality control (publication bias) and avoidance of duplicates. While we usually register systematic reviews prior to conductance in PROSPERO this has not been done for this review. We provided this information (no registration) in the PRISMA checklist (Additional file 1) and added the following sentence at the end of the limitations paragraph: “Finally, we did not register our review with PROSPERO.”

Reviewer’s comment:

About the study selection, I would ask a k-agreement between reviewers. Anyway the process of articles to be included and data extraction is well performed.

Authors’ response:

Unfortunately, we cannot calculate Cohen’s Kappa for this review, because we saved only the final agreements on inclusion and exclusion decisions. However, as presented in the methods we
piloted the study selection process. Based on this pilot selection, we assume that there was a good agreement for the rest of the selection process.

Reviewer’s comment:

Down and black scale for risk assessment of bias would be of interest and recommended.

Authors’ response:

For assessing risk of bias in non-randomized studies the Cochrane Handbook Version 5.1.0 recommends both, the Downs and Black instrument (Downs 1998) and the Newcastle Ottawa Scale (NOS) (Wells 2008). We choose the Newcastle Ottawa scale (Additional file 3).

Reviewer’s comment:

Risk of bias should be analyzed in its chapter. Above all by adding: check supplementary material #3 in its chapter.

Authors’ response:

We believe that the reviewer suggests that we should include a separate section dedicated to risk of bias. In order to highlight the risk of bias topic in the manuscript we decided to rename the first subsection in the results section to “Study characteristics and risk of bias”. At the end of this subsection, we added the following paragraph that describes the risk of bias and refers to the supplementary material.

„Among the 19 selected studies, all six RCTs and 12 observational propensity score-matched studies were rated low risk of bias. Only one observational propensity score-matched studies was rated as moderate risk of bias {Hannan, 2016 #280}. Detailed risk of bias assessments for all included studies are presented in Additional file 3.”

Reviewer’s comment:

Very good organization of the tables and format.

Authors’ response:

Thank you.
Reviewer’s comment:

I would ask the authors to justify the choice of random effect model with few sentences.

Authors’ response:

We calculated both random- and fixed-effects models (see forest plots Figure 2 and Figure 3, Additional file 8). Since we anticipated clinical heterogeneity across studies, we report only results from random-effects meta-analysis in the manuscript. We added this information to the methods section (subsection Data synthesis and analysis).

Reviewer’s comment:

I would ask author to suggest and discuss other variables that could help in choice of the best treatment and to which ways future research could be addressed; first according to their experience if possible, than trying to understand which variables could influence in the different outcomes if it is researchable in the literature. For example, I could be the responsible of the surgery team. I have to choose between the two kinds of intervention. By a new title, I could quickly read about the result.

Authors’ response:

We added the following text to the discussion:

“Guidelines recommend the decision between TAVI and SAVR to be made by the Heart Team {Baumgartner, 2017 #304;Nishimura, 2017 #312}. Beyond risk scores associated with outcome data like mortality, the members of the Heart Team have to consider individual patient characteristics including frailty, impaired mobility, aortic sclerosis, chest deformation, and previous chest radiation. In addition, comorbidities requiring additional interventions like mitral or tricuspid valve disease, coronary artery disease, and ascending aortic aneurysm {Cahill, 2018 #313}. Despite the variety of comorbidities complicating the decision for the best procedure, ongoing research has a strong focus on patients with low surgical risk or patients with moderate aortic stenosis and reduced left ventricular function in order to extend the indication for TAVI.”

Reviewer’s comment:

In the conclusion chapter I would check for more details about variables that could influence the outcome. This would be of aid in everyday clinical practice decision.
Authors’ response:

We added the following text to the conclusion in the main text: “Beyond short and long-term mortality, the Heart Team has to consider patients’ preferences, clinical characteristics, anatomical and technical aspects and cardiac conditions requiring concomitant interventions for an informed decision on choice of treatment.”

We also revised the conclusion in the abstract accordingly: “Given similar mortality risks but different patterns of adverse events, the choice between TAVI and SAVR remains an individual one.”

Reviewer #2

In their review authors compare efficacy and safety of transcatheter aortic valve implantation (TAVI) with other available methods to correct severe aortic valve stenosis, which is gaining progressively more importance for those patients that cannot undergo invasive surgery. Their results are substantially similar to the previous reviews but they provide an update of the most recent literature with a well conducted meta-analysis. Moreover, the manuscript is well written in a good quality English, and for these reasons in my opinion is amenable for publication. However, some minor revisions/suggestions could be taken into account before the paper is accepted:

Reviewer’s comment:

The title (Outcome after transcatheter aortic valve implantation: a systematic review and meta-analysis) does not reflect the real aim of the review and a more precise title should be chosen (e.g. Comparison of transcatheter aortic valve implantation with other approaches to aortic valve stenosis: a systematic review and meta-analysis).

Authors’ response:

Many thanks for the suggestions. We’d be happy to change the title accordingly.
Reviewer’s comment:

Introduction, line 68-70, the authors state that one of the limitation of a previous study was the possible bias due to the combined treatment with medical therapy and BAV, getting the reader understand that they could provide in the review an unbiased comparison of TAVI vs either MT/BAV alone. However, this review analysed only two studies that compared TAVI and MT/BAV, none considering one of the alternative approaches alone. Please change or remove this observation.

Authors’ response:

Thank you very much for raising this point. We deleted this sentence.

Reviewer’s comment:

In results section, when discussing efficacy of TAVI vs SAVR authors analyse one year mortality in 17 studies and 30-days mortality in 13 studies (I think due to follow-up duration reasons). Please explain it in the text.

Authors’ response:

We added the following text to the Results section (subsection Study characteristics and risk of bias) to address this issue: “Because of varying study durations and endpoints, the number of included studies in the respective meta-analyses varied.”

Reviewer’s comment:

In a same fashion, in the Safety (TAVI vs SAVR) paragraph comparisons take into account a different number of studies but authors do not specify the selection criteria (I think it is due to the lack of some specific-risk assessment in studies evaluated). Please explain.

Authors’ response:

We already mentioned the variation of follow-up duration in the results section (subsection Study characteristics and risk of bias) as follows: “The shortest follow-up period was one month {D’Onofrio, 2013 #71; Repossini, 2017 #306}, whereas the longest was 5 years {Thyregod, 2015 #247}.” The detailed numbers of studies in every analysis are presented in the forest plots. A detailed description of the number of studies for every investigated endpoint did not seem appropriate to us, since it would require a lot of text and would not add much to the understanding of the manuscript. However, to clarify this issue more precisely we added the following sentence to the results section (subsection Study characteristics and risk of bias):
“Because of varying study durations and endpoints, the number of included studies in the respective meta-analyses varied.”

Reviewer’s comment:
In results, Efficacy (TAVI vs MT), line 229-230, this is interpretation of results, please move the sentence in discussion

Authors’ response:
We moved this sentence to the discussion section.

Reviewer’s comment:
In results, Safety (TAVI vs SAVR), line 257-263, interpretation of heterogeneity, should be part of the discussion

Authors’ response:
We moved the paragraph to the discussion.

Reviewer’s comment:
In results, Safety (TAVI vs SAVR), line 266-267, this sentence has been already reported before, it sounds redundant

Authors’ response:
We agree that this information is redundant. We deleted this sentence.

Reviewer’s comment:
Table 1, eligibility criteria, design of the study selected, one of the possible study is represented by non-randomized controlled trial but among the 19 study selected there are not NRCT. Could it be removed from the table?

Authors’ response:
Table 1 presents our a priori defined eligibility criteria. At this point, we cannot change them anymore.
Reviewer’s comment:

Finally, some of the analysed studies (the most recent) evaluated TAVI performance and outcomes on low-intermediate risk patients. It would be interesting a sub-group comparison of efficacy and safety of these arms with SAVR and high risk TAVI to see if any difference can be noted. Did authors performed this analysis?

Authors’ response:

We conducted a subgroup analyses to compare 30 days and one-year all-cause mortality in high and low or intermediate risk populations. We provided results in the main text (Methods section, subsection Data synthesis and analysis) and corresponding forest-plots (see Additional file 7).

“Subgroup analysis of RCTs and propensity score-matched observational studies with high-risk patient populations yield similar all-cause mortality after TAVI and SAVR at 30 days (5.4% versus 5.7%; RR 0.92; 95% CI: 0.65 to 1.31; I2=37.0%) and one year (18.5% versus 18.1%; RR 1.04; 95% CI: 0.85 to 1.27; I2=44.1%). Random-effects meta-analysis of studies with intermediate- or lower-risk patients yields no statistically significant difference of those treated with TAVI compared to SAVR at 30 days (3.9% versus 3.5%; RR 1.17; 95% CI: 0.84 to 1.63; I2=40.5%) and one year (11.1% versus 10.8%; 1.03; 95% CI: 0.90 to 1.18; I2=0%) (Additional file 7).”

Reviewer #3

Reviewer’s comment:

1. Who are investigators who performed search in "We searched the electronic databases", need to be very specify?

Authors’ response:

We added initials of the information specialist (BW) to the text (Methods, subsection Data sources and searches):

“An experienced medical information specialist (BW) searched the electronic databases MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials via Ovid on January 27, 2017 with an additional update performed on June 6, 2017.”
Reviewer’s comment:

2. "All searches in electronic databases were conducted by an experienced medical information specialist" This means only 1 investigator performed the search?

Authors’ response:

This is correct. One experienced medical information specialist (BW) performed all literature searches. To clarify this, we revised the respective sentence as follows. (Methods, subsection Data sources and searches):

“An experienced medical information specialist (BW) searched the electronic databases MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials via Ovid on January 27, 2017 with an additional update performed on June 6, 2017.”

Reviewer’s comment:

3. "Two investigators independently rated the risk of bias"; please specify by the initials.

Authors’ response:

We added initials (HA, GW) to the text (Methods, subsection Risk of bias assessment and certainty of evidence)

“Two reviewers (HA, GW) assessed the risk of bias of included studies. For risk of bias assessment of RCTs, we used the Cochrane Risk of Bias Tool {Higgins J, 2008 #25} and the Newcastle-Ottawa-Scale (NOS) for observational studies {Deeks, 2003 #251}.”

Reviewer’s comment:

4. This review is not registered online? Please clarify and include this point in limitation of the study.

Authors’ response:

We are aware that preceding registration of systematic reviews in PROSPERO is important for transparency, quality control (publication bias) and avoidance of duplicates. We added this information to the limitations.
Reviewer’s comment:

5. Strongly suggest the investigators proving PRISMA Checklist in Online

Authors’ response:

We provided the PRISMA checklist as Additional file 1 (Methods section, first paragraph)

Reviewer’s comment:

6. Currently, I2 was showed in Figures, but investigators selectively included in the results of manuscript only when I2 was not significant. Strongly suggest mentioning all I2 in the results.

Authors’ response:

We added I2 to all results of the meta-analyses.

Reviewer’s comment:

7. A multivariate meta-regression model is suggested when there are significant heterogeneities.

Authors’ response:

We explored the feasibility of performing meta-regression analysis in case of high statistical heterogeneity. High heterogeneity was noted for major vascular complication, major bleeding and new pacemaker implantation at 30 days. However, we were facing a study number problem: The highest number of studies were noted for vascular complications (k=10) and new pacemaker implantation (k=14). The incomplete reporting of potential co-variates further limited the number of studies for meta-regression analysis. Since both observational and randomized studies were included in meta-analyses we would need to include study design as a co-variate in addition to the independent variable of interest. In this case, we would not fulfill the consensus criterion for the minimum of 10 studies for each covariate. For this reason, we would prefer not to present meta-regression analysis in this manuscript.
Reviewer’s comment:

8. We recommend the authors apply the ROBINS-I (Risk of Bias in Nonrandomized studies of Interventions) tool. The authors already applied the Newcastle Ottawa Scale, which is a validated tool and was an acceptable choice. However, to enhance the reproducibility and comparability of this review to future reviews of a similar topic (possibly an update of this review) I recommend including a risk of bias assessment using ROBINS-I, since it is the newest and most robust method of assessing risk of bias in systematic reviews/meta-analyses.

Authors’ response:

We agree that the ROBINS-I tool is the newest one to assess risk of bias in non-randomized studies. The Cochrane Scientific Committee (https://methods.cochrane.org/robins-i-tool) recommends this new tool with the Newcastle Ottawa scale as a valid alternative. We selected the Newcastle Ottawa scale, since it is a validated, accepted and widely used tool to assess risk of bias in observational studies. For a future update of this systematic review, we will definitely consider reviewers’ suggestions to use ROBINS-I for risk of bias assessment in observational studies.

Reviewer’s comment:

9. The authors should address publication bias and provide both a funnel plot and Egger test result. Please perform Egger test.

Authors’ response:

We performed Egger’s test for asymmetry of the funnel plots and added text to the manuscript: Methods section, subsection Data synthesis and analysis: “We assessed potential publication bias with Egger’s tests and the visual interpretation of funnel plots.” Results section, subsection Efficacy and effectiveness, TAVI compared to SAVR: “Egger’s test and visual inspection of funnel plots did not suggest publication bias (see Additional file 5).” In addition, we added results of Egger’s test to Additional file 5.

Reviewer’s comment:

10. For transparency, I would suggest making the data for this review publicly available, possibly through the Open Science Framework (osf.io). A link to the OSF page with all the
information can be included in this manuscript. Items to include: list of excluded studies, commands for statistical analysis, spreadsheets or data used for the meta-analyses, etc. Making data publicly available will promote the reproducibility of the review and is best practices for systematic reviews and meta-analyses.

Authors’ response:

We agree that public availability of data ensures transparency. Therefore, we provided patients’ characteristic and outcome data of individual studies in Additional file 4 and included raw data (number of events and patients at risk) for meta-analysis in forest-plots (Figure 2 and 3, Additional file 8). Based on this information readers could easily recalculate and verify our findings. As suggested, we have added a new list of references excluded on full-text level with reasons to Additional file 2. Under the declarations section we provided following statement: “All data generated or analysed during this study are included in this published article and its supplementary information files.”

Reviewer’s comment:

Otherwise, the authors present a thoughtful and well-written systematic review and meta-analysis.

Authors’ response:

Thank you.